REMARKS

The Office Action dated January 2, 2004, has been received and reviewed. Claims 1-29 and 32 are pending in the present application. Claims 27-29 and 32 have been withdrawn from consideration by the Examiner. Claims 1-26 stand rejected. Applicants have included a new abstract with the present response. Applicants respectfully request reconsideration of the application in view of the amendments made and the arguments below.

I. Specification Objections

Applicants have amended the specification as suggested by the Examiner to correct for spelling errors and to be consistent with the disclosure. Applicants have also included a new sequence listing. Accordingly, Applicants submit that the specification is in proper order.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-26 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully disagree with this assertion for the reasons that follow.

Applicants have amended claim 1 to clarify that the relationship between the compound and the receptor/reporter fusion protein. Specifically, the preamble to claim 1 has been amended to clarify that the compound has an effect on a membrane receptor. Furthermore, Applicants have included step (a) which recites that the fusion protein comprises a membrane receptor segment and a reporter segment. Applicants have also amended step (b) which recites that the change is detected by detecting a signal from the reporter segment. Accordingly, Applicants respectfully submit that claim 1 is now in condition for allowance and request withdrawal of the 35 U.S.C. § 112 rejections to claim 1.

Claim 6 has been amended as suggested by the Examiner to remove the language "or can in themselves disrupt such interactions". Applicants respectfully request reconsideration and withdrawal of the rejections to claim 6.

Claim 8 has been amended as suggested by the Examiner to remove the term "therapy". Applicants respectfully request reconsideration and withdrawal of the rejections to claim 8.

Claim 4 has been canceled without prejudice or disclaimer thus mooting this rejection.

Claim 5 has been amended to clarify the activity. Specifically, the claim now recites that the assay detects an increase in activity of the reported segment of the fusion protein. Applicants respectfully request reconsideration and withdrawal of the rejections to claim 5.

Claims 14-16 and 18-20 stand rejected as allegedly lacking antecedent basis. Applicants have amended these claims to recite reporter segment as is recited in claim 1. Applicants respectfully request reconsideration and withdrawal of the rejections to claims 14-16 and 18-20.

Claim 12 has been amended to clarify that the compound binds to the receptor segment of the fusion protein. Applicants respectfully request reconsideration and withdrawal of the rejections to claim 12.

Claim 15 has been amended to recite that the functionality of the membrane receptor segment is substantially unaffected by the reporter segment. Applicants respectfully request reconsideration and withdrawal of the rejections to claim 15.

The phrases "or the like" and "such as" have been taken out of claims 22-23. Applicants respectfully request reconsideration and withdrawal of the rejections to claim 22-23.

Claim 24 has been amended to correct for inconsistent language and to have proper antecedent basis. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to claim 24.

Claim 3 has been canceled without prejudice or disclaimer thus mooting this rejection.

Claims 7-8 stand rejected as allegedly failing to further limit the subject matter of the previous claim. Applicants respectfully disagree with this assertion as any given compound tested may also have no effect on the membrane receptor. Therefore, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph rejections to claims 7-8.

In view of the foregoing, Applicants respectfully submit that the claims are now in condition for allowance and the same is respectfully requested.

III. Rejections under 35 U.S.C. § 102 (b) and (e)

A. Barak et al.

Claims 1, 8-10, 13-17, 20-22 and 24 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Barak et al. (Molec. Pharma. 2, 177, 1997). Applicants respectfully traverse this rejection as set forth below.

Case law holds and the M.P.E.P. states that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Additionally, anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000).

Applicants submit the amendments made to Claim 1 include the elements of claim 11 which was not rejected under 35 U.S.C. § 102(b). Barak et al. merely describes fusions between beta2-andrenergic receptor and GFP. The receptor protein used are wild type proteins. The claims of the present application recite a constitutively active mutant. Applicants submit that because all of the elements of the present claims are not found in the teachings of Barak et al., the claims are not anticipated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) to claims 1, 8-10, 13-17, 20-22 and 24.

B. Siegel et al.

Claims 1-3, 6-9, 13-17, 20 and 24 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Siegel et al. (U.S. Patent No. 6,660,844). Applicants respectfully traverse this rejection. Similar to above, Siegel et al. fails to anticipate a constitutively active mutant. Siegel et al. also fails to teach a fusion protein comprising a membrane receptor segment and a reporter segment wherein the membrane receptor segment is a constitutively active mutant receptor. Applicants submit that because all of the elements of the present claims are not found in the teachings of Siegel et al,. the claims are novel. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) to claims 1-3, 6-9, 13-17, 20 and 24.

IV. Rejections under 35 U.S.C. § 103(a)

A. Barak et al and Leurs et al.

Claims 1, 9-12 and 24-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Barak et al. in view of Leurs et al. (TIBS, 23 418 1998). Applicants traverse this rejection for the amended claims for the reasons set forth below.

To establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has also stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Furthermore, as affirmed by the Court of Appeals for the Federal Circuit in *In re Sang-su Lee*, a factual question of motivation is material to patentability, **and cannot be resolved on subjective belief and unknown authority**. *See In re Sang-su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Respectfully, as will be discussed below, the Official Action fails to meet the requirements for a prima facie showing of obviousness under § 103.

As noted above, Barak et al. does not teach or suggest the use of constitutively active mutants. Furthermore, Leurs et al. fails to teach or suggest the elements of the present invention. Applicants submit that Leurs et al. describes various properties of constituently active mutants (CAMs) of G-protein coupled receptors but make no suggestion as to how these properties could be usefully applied. Furthermore, Leurs et al. fails to contain any motivation to generate a fusion protein between a CAM and a reporter protein, much less use such a fusion in an assay as claimed in the present application. Applicants submit that the present invention is the first to

realize the properties of CAMs that can be exploited to provide a test for compounds which modulate membrane receptor protein activity. Applicants note that CAM has a short half-life compared to a wild-type receptor. Thus, although the CAM receptors are constantly being produced, they are also constantly being internalized from the membrane into the cell and are being destroyed at a much higher rate than the wild-type receptor. Leurs et al. fails to suggest or teach that these properties can be exploited to produce the assay as presently claimed. Leurs et al. fails to teach or suggest that CAMs can be successfully used in an assay to determine the effect of a test compound on a membrane receptor. Because of the inherent instability of CAM receptors, the effect of any given test compound on the activity of a Cam receptor/reporter fusion protein will be much greater than it would be as compared to the activity of a wild type receptor/reporter fusion protein. Thus, Leurs et al. fails to contain the motivation to combine itself with Barak to teach the elements of the present claims. The assay as claimed in claim 1 can be made much more sensitive than that taught or suggested by Leurs et al. Accordingly, Applicants respectfully request reconsideration of the rejection of Claims 1, 9-12 and 24-36 under 35 U.S.C. § 103(a).

B. Siegel et al., Barak et al. and Leurs et al.

Claims 1-5, 9-12 and 24-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel et al. in view of Barak et al. and Leurs et al. Applicants traverse this rejection for the amended claims for the following reasons. Applicants submit that as noted above, neither Barak et al. nor Leurs et al. either alone or in combination teach or suggest the elements of the claims of the present application. Furthermore, Siegel et al. as noted above, fails to disclose all of the elements of the claims of the present invention. Siegel et al. provides a kit for determining the presence of an activity in a sample, including either a chimeric protein of the invention, or a nucleic acid sequence encoding a chimeric protein of the invention. The example provided by Siegel et al. illustrates a responsive polypeptide that is a voltage-gated ion channel and an optically active polypeptide, a deletion mutant of GFP. In contrast, the claims of the present invention recite an assay for detecting an effect a compound has on a membrane receptor by adding the compound to a cell expressing a membrane receptor/reporter fusion protein, the fusion protein comprising a membrane receptor segment and a reporter segment; and detecting any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment;

wherein the membrane receptor segment is a constitutively active mutant receptor. Sigel et al. fails to teach or suggest any such assay. Furthermore, Siegal et al. in view of Barak et al. and Leurs et al. fail to teach or suggest such an assay. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejections to claim 1-5, 9-12 and 24-26.

C. Barak et al. and Bryan et al.

Claims 1-2, 13-14 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Barak et al. in view of Bryan et al., U.S. Patent No. 6,232,107. Applicants traverse this rejection for the amended claims for the following reasons. As noted above, Barak et al. fails to teach or suggest the elements of the present invention as presently claimed. Similarly, Bryan et al., either alone or in combination with Barak et al., fails to teach the elements of the claims of the present invention. Bryan et al. provides isolated nucleic acids that encode fluorescent proteins and nucleic acids that encode luciferases. Bryan et al. does not teach or suggest the assay as claimed which detects any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment; wherein the membrane receptor segment is a constitutively active mutant receptor. Therefore, claim 1 and its subsequent dependent claims are not obvious in view of Barak et al. and Bryan et al. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejections to claims 1-2, 13-14 and 23.

D. Siegel et al. and Bryan et al.

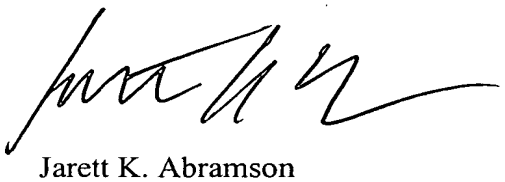
Claims 1-2, 13-14, 18-19 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel et al. in view of Bryan et al. Applicants traverse this rejection for the amended claims for the following reasons. As noted above, both Siegel et al. and Bryan et al. fail to teach or suggest the elements of the claims of the present application either alone or in any combination. Furthermore, the combination of Siegel et al. and Bryan et al. would still not teach or suggest the elements of the present invention as again they both fail to teach or suggest an assay which detects any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment, wherein the membrane receptor segment is a constitutively active mutant receptor as presently claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejections to claims 1-2, 13-14, 18-19 and 23.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,

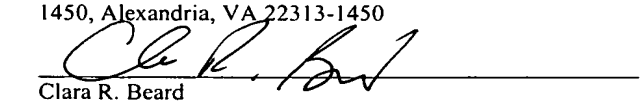


Jarett K. Abramson
Registration No. 47,376

USPTO Customer No.: 20792
Myers Bigel Sibley & Sajovec, P.A.
Post Office Box 37428
Raleigh, NC 27627
Telephone (919) 854-1400
Facsimile (919) 854-1401

CERTIFICATE OF EXPRESS MAILING

"Express Mail" mailing label number: EV 193584208 US
Date of Deposit: April 8, 2004
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450



Clara R. Beard

increase in fluorescence in intracellular vesicles which by co-immunolocalisation studies with an anti-transferrin antiserum are shown to be endosomes. The decrease in fluorescence observed by ~~micrioplate~~ microplate fluorimetry following internalization of the fusion protein may be due in part to receptor degradation but may also be due to a fluorescence quenching event as a consequence of receptor concentration within the acidic environment of the endosome compartment. However, this decrease in fluorescence caused by agonist ligands such as isoprenaline is concentration dependent and the half maximal drug concentrations required to cause this effect is in agreement with the values obtained in traditional second messenger analysis studies.

Thus the example discloses a novel screening system for compounds with either agonist, neutral antagonist or inverse agonist activity at the β_2-adrenoceptor in which compound activity results in a change in the fluorescence characteristics of cells expressing a β_2-adrenoceptor-GFP fusion protein. The change in the fluorescence characteristics can be measured by either a change in cellular localisation using the confocal microscope, or by a change in total cellular fluorescence as measured in a 96-place fluorimeter. Using confocal microscopy as the detection system, ~~agonist ligand~~ antagonist/inverse would cause an increase in cell surface fluorescence of the CAM GPCR/GFP fusion protein while ~~antagonist/inverse~~ agonist ligand agonist ligands cause an increase in internalization of a WR GPCR/GFP fusion protein. Using microplate fluorimetry as the detection